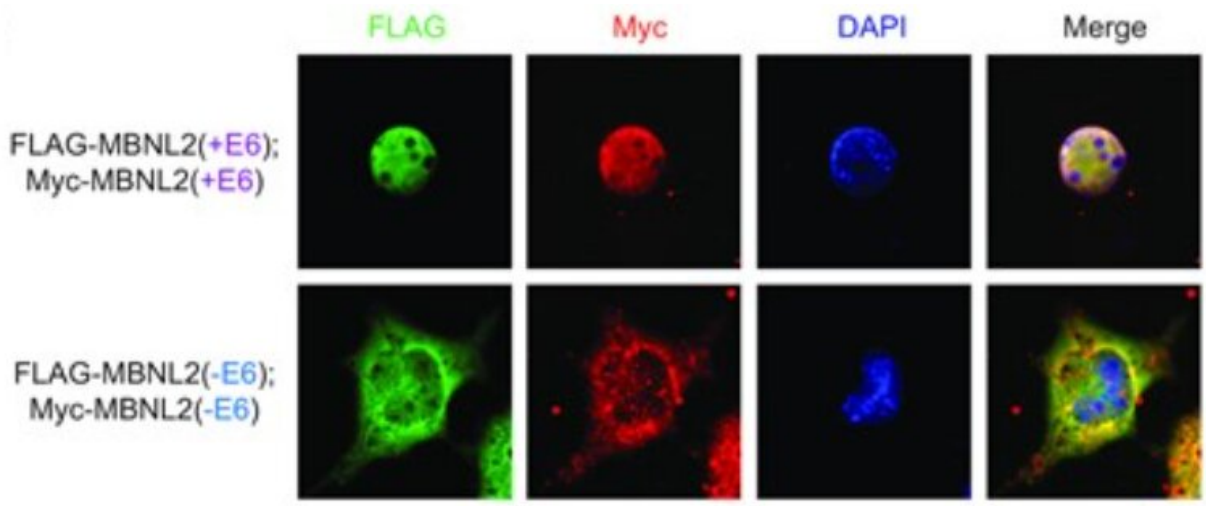
How to compensate for loss of gene function? Think alternative splicing

February 21 2023, by Ana María Rodríguez



Immunofluorescent images of single COSM6 cells expressing MBNL2(+E6) and MBNL2(–E6). Inclusion of Exon 6 results in a predicted nuclear localization signal. The cells were stained using DAPI (blue) and anti-FLAG (green) and anti-Myc (red) antibodies. Credit: *Nucleic Acids Research* (2023). DOI: 10.1093/nar/gkac1219

Living organisms have a knack for persisting in the face of challenges. For instance, when genes malfunction, organisms may be able to compensate by activating redundant genes with similar functions, called paralogs.

One example of such compensation are two genes of the muscleblind-

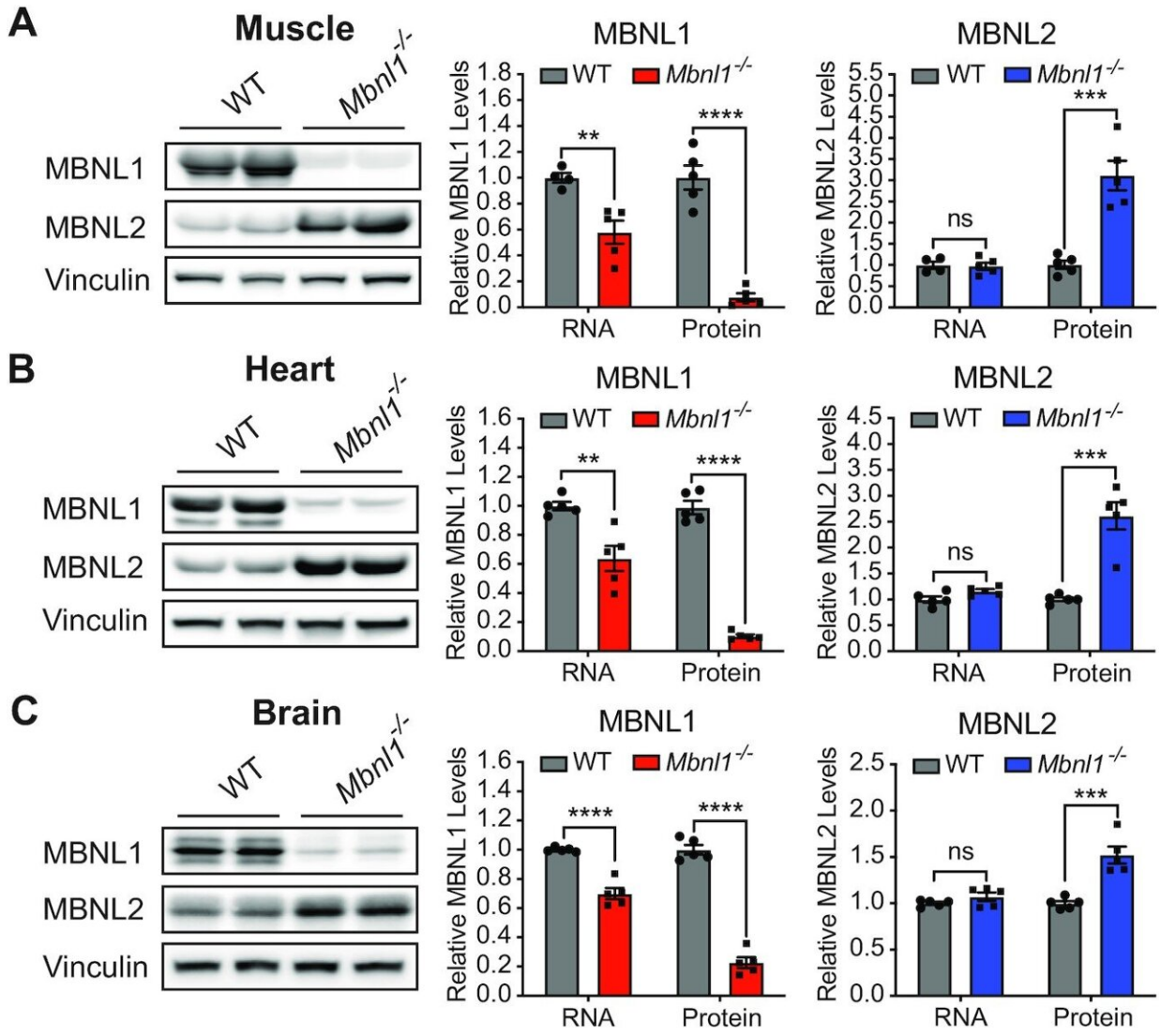
like (MBNL) family of RNA-binding proteins that lose their function in Myotonic Dystrophy Type 1, the most common cause of adult-onset muscular dystrophy. Loss of MBNL1 increases the levels of its paralog MBNL2 in tissues where protein expression is low, allowing MBNL2 to functionally compensate for MBNL1 loss. In animal models, loss of one paralog results in no or only minor functional consequences, whereas loss of both paralogs leads to a severe condition and lethality.

A paper on this topic is published in the journal *Nucleic Acids Research*.

"Although this form of compensation for loss of gene function has been widely observed, the underlying molecular mechanisms and roles in preventing or modifying disease severity are not well understood," said first author Dr. Larissa Nitschke, a postdoctoral associate of pathology and immunology in Dr. Thomas A. Cooper's lab at Baylor College of Medicine. "In this study, we discovered how loss of MBNL1 leads to the compensatory increase of MBNL2 protein."

MBNL proteins are deeply involved in RNA processing, including alternative splicing, a process that allows cells to make many different proteins from a limited number of genes.

"To make proteins, genes in the DNA are transcribed into RNA, which is then translated into protein. Before RNA is translated into protein, it is processed and the fragments spliced in a certain way," said Cooper, R. Clarence and Irene H. Fulbright Chair and S. Donald Greenberg Chair in Pathology. He also is the corresponding author of the work. "In almost all genes, the RNA is spliced in more than one way. That is alternative splicing; it allows one gene to make many different proteins. It would be like putting together different bracelets by combining a limited number of beads in unique ways."



Loss of MBNL1 increases MBNL2 protein but not RNA levels in skeletal muscle, heart and brain. Representative western blot and quantification of MBNL1 and MBNL2 protein and RNA levels in (A) skeletal muscle, (B) heart and (C) brain of $Mbnl1^{+/+}$ (WT) and $Mbnl1^{-/-}$ mice. For the western blot quantifications, MBNL1 and MBNL2 protein levels were normalized to vinculin. Note that we found that the MBNL1 antibody used cross reacts with MBNL2 (data not shown), which we believe is the residual band in $Mbnl1^{-/-}$ tissues. For the RT-qPCR quantifications, Mbnl1 and Mbnl2 RNA levels were normalized to Gapdh. For each assay, a minimum of four replicates were performed. Simple comparisons used Student's t-test. In each case, **, ***, **** and ns denote P

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